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published in
JAMA - Journal of the American Medical Association
2018

DOI (link to publisher)
10.1001/jama.2018.17824

document version
Publisher's PDF, also known as Version of record

VIEWPOINT

The Challenges of Improving Treatments for Depression

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In the past few decades substantial progress has been made in the research and development of treatments for major depression. Many different types of medications and psychotherapy are currently available and rigorous studies have shown that antidepressants are more effective than placebo,[1] and several types of psychotherapies are more effective than waiting list or other controls.[2] These findings suggest that many patients with depression can be successfully treated. Based on these significant and positive effects, many of these treatments are included in treatment guidelines and are widely used in clinical practice. However, not all patients with depression recover with available treatments and several important challenges need to be resolved to improve existing treatments and to increase the number of patients who benefit from them.

Spontaneous Recovery and Placebo Effects

An important challenge is the high rates of spontaneous response and placebo effects. More than half of patients who receive antidepressants or psychotherapy respond to treatment. However, response rates are also high when patients receive placebo or no treatment. In a meta-analysis that included 44 240 patients from 177 studies, 54% of patients responded to antidepressants, whereas 38% responded to placebo.[3] Comparable numbers have been reported for psychotherapies with response rates of 54% compared with response rates of 41% across control conditions.[4] Patients with depression who do not seek care show comparable response rates. These findings differ when other outcomes, such as remission or significant clinical change, are used. That does not, however, change the basic challenge that a substantial proportion of patients who improve with medication or psychotherapy would have recovered without treatment or with placebo. This poses substantial challenges for investigators and clinicians.

> Nevertheless, for patients with depression many do not benefit from treatment, and some only partially benefit or only experience short-term improvement.

Individuals who respond to medication will probably continue to use them for at least several months, even with the risk of adverse effects. Patients who respond to psychotherapy invest many hours and make considerable efforts during their treatment. For a majority of patients who respond to treatment, the potential adverse effects of medications and the time investment in psychotherapy might not be necessary to get better. However, it is not possible yet to predict which patients will recover spontaneously or will respond to placebo, although innovative machine learning techniques and other biological markers may be helpful in the future.

Spontaneous recovery also complicates the validity of clinical knowledge as well as research about treatments. Because many patients recover while receiving treatment, clinicians and patients are inclined to think that the treatment is what made them better. However, because many patients also would have recovered without treatment, clinical judgements are not necessarily related to treatment effect.

Nonresponse

In contrast to response to drug or placebo, a considerable group of patients are difficult to treat or do not respond to treatment. Although patients may respond to another drug after failure to respond to an initially prescribed drug, the chance of successful response is almost halved with every new treatment tried.[5] Even after trying several different treatments, a substantial proportion of patients do not respond. One estimate suggests that approximately 30% of patients with depressive disorders have a chronic course with limited response to treatment.[6]

Another challenge is that the effects of treatment are probably overestimated. The relapse rates for patients who respond are very high (estimated at about 50% over 2 years),[7] there is limited evidence for long-term effectiveness, and there are the problems of publication bias, sponsorship bias, and other sources of bias. Clinicians may have an optimistic view that these problems have little influence on outcomes or have a pessimistic view that no relevant treatment effect remains. In reality, the extent to which these factors affect outcomes is unknown.

How to Improve Treatments?

Worldwide, an estimated 330 million people have depression, which is linked with considerably diminished role functioning and quality of life, medical comorbidity, excess mortality, and high economic costs.[8] Thus, addressing current therapeutic challenges and improving available treatments are critically important, regardless of the true effects of these treatments. How can this be done?

Additional research on the causes and etiological processes leading to depression is needed. The focus should be on which patients will respond to treatment, which could lead to the development of better and more

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targeted treatments for specific groups of patients. This may result in new approaches for preventing depression. However, this will take time and long-term investments.

A straightforward approach in the short-term is to develop treatments that are more effective than the current ones in acute phase depression. However, many drugs and psychotherapies have been developed over the past decades, and there is little evidence that one drug or psychotherapy is substantially more effective than the others. It is therefore unlikely that newly developed drugs and therapies will be substantially better than the ones that are currently available.

A potentially viable approach with respect to spontaneous recovery is to minimize treatments and reduce unnecessary resource use because many patients with depression will recover spontaneously, regardless of treatment. Clinicians already use a "watchful waiting" approach, by encouraging patients to wait before starting a treatment. Another option is to offer internet-based or other self-help interventions that involve no or minimal support from professionals, preferably in stepped-care models allowing patients who do not respond to these interventions to step up to more intensive treatment. Considerable evidence indicates that these internet-based interventions are effective and require less resources.[9] Another option may be to clearly explain to patients what the chance for recovery is from treatment, from placebo, or from no treatment. This may stimulate patients with milder disorders to wait before starting treatment, whereas patients with severe disorders will probably prefer to initiate treatment.

There are also several priorities for patients with depression who have high relapse rates or those who do not respond to treatments. One important priority is to further examine relapse prevention. In routine practice, this often consists of maintenance treatment with drugs. However, convincing evidence indicates that psychological interventions can reduce relapse rates considerably, although these interventions are seldom implemented in routine care.

Another priority is to increase research on the treatment of chronic and resistant depression. Fortunately, these conditions are increasingly the focus of drug trials, and some promising new medications are being tested, such as ketamine.[10] However, few psychological treatments are available that are specifically designed for chronic depression. The development of such therapies should have more priority than developing new therapies for acute depression that almost certainly will show comparable effects as already existing treatments.

Answering the Challenge

Evidence-based treatments can make a substantial difference in the lives of many patients. Nevertheless, for patients with depression many do not benefit from treatment, and some only partially benefit or only experience short-term improvement. Furthermore, a considerable group of treated patients would have also recovered without treatment. The group of patients in between these extremes are the ones who currently benefit from available treatments, but they are still a minority of all patients. Because of the public health effects of depression and the enormous related adverse effects on the quality of life of patients, it should be a priority to search for methods to increase the number of patients who benefit from treatment and in this way reduce the burden of depression.

ARTICLE INFORMATION

Published Online: November 30, 2018. doi:10.1001/jama.2018.17824

Conflict of Interest Disclosures: No disclosures were reported.

REFERENCES

1. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet*. 2018; 391(10128):1357-1366. doi:10.1016/S0140-6736(17)32802-7

2. Barth J, Munder T, Gerger H, et al. Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. *PLoS Med*. 2013;10(5):e1001454. doi:10.1371/journal.pmed.1001454

3. Levkovitz Y, Tedeschini E, Papakostas GI. Efficacy of antidepressants for dysthymia: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry*. 2011;72(4):509-514. doi:10.4088/JCP.09m05949blu

4. Cuijpers P, Karyotaki E, Weitz E, Andersson G, Hollon SD, van Straten A. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. *J Affect Disord*. 2014;159:118-126. doi:10.1016/j.jad.2014.02.026

5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163 (11):1905-1917. doi:10.1176/ajp.2006.163.11.1905

6. Murphy JA, Byrne GJ. Prevalence and correlates of the proposed *DSM-5* diagnosis of chronic depressive disorder. *J Affect Disord*. 2012;139(2): 172-180. doi:10.1016/j.jad.2012.01.033

7. Vittengl JR, Clark LA, Dunn TW, Jarrett RB. Reducing relapse and recurrence in unipolar depression: a comparative meta-analysis of cognitive-behavioral therapy's effects. *J Consult Clin Psychol*. 2007;75(3):475-488. doi:10.1037/0022-006X.75.3.475

8. Bloom DE, Cafiero E, Jané-Llopis E, et al. The global economic burden of noncommunicable diseases. Geneva, Switzerland: World Economic Forum. http://apps.who.int/medicinedocs/en/m/abstract/Js18806en. Published September 2011. Accessed November 18, 2018.

9. Andrews G, Basu A, Cuijpers P, et al. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. *J Anxiety Disord*. 2018;55: 70-78. doi:10.1016/j.janxdis.2018.01.001

10. Wilkinson ST, Sanacora G. Considerations on the off-label use of ketamine as a treatment for mood disorders. *JAMA*. 2017;318(9):793-794. doi:10.1001/jama.2017.10697